PULMONARY HYALINE DISEASE OF INFANTS*

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IN RECENT YEARS considerable emphasis has been placed on the etiology and pathogenesis of neonatal pulmonary failure. Our interest in this problem was first aroused by a paper of Kaufman and Spiro[1] in which they described, in support of MacMahon,[2] a previously unrecognized congenital malformation of the fetal lungs which they termed alveolar dysplasia. Review of our own group of stillbirths and neonatal deaths revealed several cases which resembled closely those described by these authors. We were, however, unable to agree with their conclusions, and were of the opinion that the entity described was not a congenital anomaly but a peculiar type of pulmonary collapse to which Potter[3] had given the name resorption atelectasis. In many of these cases pulmonary hyaline membranes were present as well. Resorption atelectasis and hyaline membrane formation constitute the main histological features of a disease entity which apparently has a typical clinical picture and has been referred to by Potter[4] as pulmonary hyaline disease of infants.

Hoccheim[5] in 1903 was the first to describe a coating of the alveolar ducts, atria, and alveoli by an irregular, but well-defined homogeneous eosinophilic material. In the past 50 years over 5,000 autopsies have been reported on newborn infants of viable gestation, of which approximately 13% showed pulmonary hyaline membranes. There is no general agreement on the terminology used, various names being applied according to the author's view of the etiology of the membrane. Some have referred to it as an asphyxial membrane, others call it a vernix membrane, and still others a hyaline or hyaline-like membrane. The original workers were of the opinion that the eosinophilic material was derived from proteins present in the vernix caseosa, or amniotic fluid. The importance of resorption atelectasis with its associated membrane formation as a primary cause of death was first stressed by Dick and Pund[6] in 1949. This fact has been re-emphasized by Potter as well.

CLINICAL-PATHOLOGICAL FEATURES OF PULMONARY HYALINE DISEASE OF THE NEWBORN

Clinically, the features observed in infants dying of pulmonary hyaline disease follow a rather consistent pattern. The lesion is found almost exclusively in liveborn infants, and is more often present in the premature and in those delivered by Cæsarean section than in full-term infants delivered *per vaginam*. The overall incidence usually quoted is 20% of newborn infants with a variation between 6 and 100% depending upon the weight of the child.

Initially there is spontaneous respiration and normal behaviour for 1-2 hours, followed by respiratory difficulty and death, usually within the first 48 hours of life. Death is considered to be the result of abnormal pulmonary ventilation produced by resorption atelectasis and the pulmonary hyaline membranes which act as a barrier to proper capillary oxygen exchange. Grossly, the lungs are uniform in appearance, firm in consistency, deep red in colour, and often weigh more than would the normal lungs of an infant of the same age and weight. Microscopic examination reveals scattered zones of dilated air spaces which are lined by an irregular layer of homogeneous, finely granular, eosinophilic material. These alternate with areas in which alveolar collapse is marked. The latter regions appear solid.

CHEMICAL NATURE OF HYALINE MEMBRANES

The exact chemical nature and the origin of the eosinophilic substance have not been established. The amino acids tyrosine and and arginine are present, and with the use of the Schiff periodic acid stain the presence of a carbohydrate complex attached to the protein is identified. Fat is stainable in varying amounts in many instances, but is entirely absent in others. The material is negative for iron, cholesterol, collagen, amyloid, elastic tissue, red cells, mucus, and bronchiolar epithelium.

PRESENTATION OF 17 CASES OF PULMONARY HYALINE MEMBRANE DISEASE

Stillbirths and neonatal deaths occurring at the Kingston General Hospital, and at the Hôtel-

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Dieu Hospital, Kingston, during the years 1948-1951, were investigated. The autopsy protocols were reviewed and the lung sections re-examined in all cases. There was no attempt to eliminate those cases showing clinical evidence of pulmonary inflammation or in which the body of the infant weighed less than 2,500 gm.

TABLE I.

INCIDENCE AND ASSOCIATED FINDINGS IN 17 CASES OF HYALINE MEMBRANE DISEASE IN INFANTS

(a) Relation to birth weight:	
300 - 1,000 gm.	2 cases
1,001 - 1,500 gm.	3 "
1,501 - 2,500 gm.	5 "
Over 2,500 gm.	7 "
Total	17 "
(b) Relation to duration of life:	
0 - 12 hours	6 cases
13 - 24 "	5 "
25 - 36 "	4 "
37 - 48 "	1 case
Over 48 "	1 case
Total	17 cases
(c) Relation to other pathological lesions:	
Hyaline membranes only	14 cases
Intracranial hæmorrhage	1 case
Hypoplasia of lungs	1 "
Hæmorrhage into adrenals	1 "
Total	17 cases

Thirty stillborn and 51 liveborn infants were included in this study. No evidence of resorption atelectasis or hyaline membrane formation was present in any of the stillborn infants, while the incidence of these changes in the liveborn infants was 33% (17 cases). Ten of the infants showing this type of atelectasis with associated hyaline membranes were born prematurely, seven having a birth weight of 2,500 gm. or more (Table I). None died within the first hour of life and, if one premature infant is excluded, the longest period of survival was 46 hours. This infant had a birth weight of 700 gm. and died on the 6th day of life, the lungs showing small areas of resorption atelectasis. Six infants died within 12 hours of birth, 15 of the affected newborn dying before the end of the first 36 hours of life (Table I). Resorption atelectasis and hyaline membranes were found without any associated significant pathological lesion in 83% of the cases; intracranial hæmorrhage, hypoplasia of the lungs, and intra-adrenal hæmorrhage were encountered in one each of the three remaining cases.

PATHOLOGICAL FEATURES OF PULMONARY HYALINE MEMBRANE DISEASE

The pathological features of pulmonary hyaline membrane disease were well defined. Grossly, the lungs were voluminous, moderately firm, and dark red or purple in colour. Some of the lung segments sank readily in water while others contained sufficient air to allow them to float. The microscopic picture was that of resorption atelectasis (Fig. 1) with scattered air-filled atria and alveolar ducts separated by apparently solid zones of tissue which proved to be formed of collapsed alveolar walls. In many segments the atria and alveolar ducts were lined by irregular layers of homogeneous eosinophilic material, the hyaline membranes; while in other regions this membrane formation was not always in evidence. High-power magnification (Fig. 2) demonstrated marked congestion of alveolar capillaries, and with care small amounts of eosinophilic granular material could be identified within some of the collapsed alveoli. The use of the reticulin stain served to demonstrate more clearly the usually ill-defined alveolar walls.

OCCURRENCE OF PULMONARY HYALINE MEMBRANES IN DISEASES OF ADULTS AND OLDER CHILDREN

Pulmonary hyaline membranes are not limited to the newborn. In a recent excellent review De and Anderson[7] have listed 21 diseases of adults and older children in which the condition has also been reported. These include: (1) influenza and influenzal pneumonia; (2) rheumatic disease; (3) bronchopneumonia; (4) war gas poisoning; (5) radiation pneumonitis; (6) sulphonamide pneumonitis; (7) poliomyelitis; (8) chickenpox; (9) subacute bacterial endocarditis; (10) metastatic carcinomatosis of the lungs; (11) lymphosarcomatosis; (12) Hodgkin's disease; (13) uræmia; (14) beryllium poisoning.

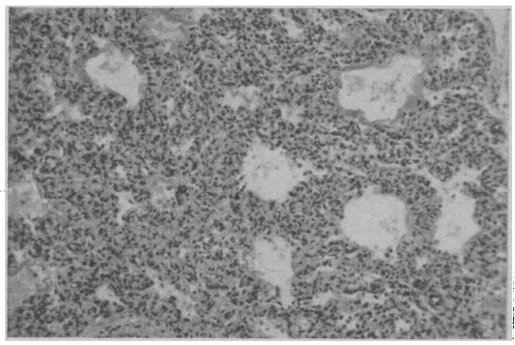
A consideration of the fact that pulmonary hyaline membranes have been discovered in so many diseases of varying etiology may be of some assistance in establishing the nature of the etiology and pathogenesis of this material. The suggested cause in practically all of the above-mentioned diseases is vascular injury with particular involvement of the alveolar capillaries. The protein material of the membranes is considered therefore to have been derived from blood.

PATHOGENESIS OF PULMONARY HYALINE MEMBRANE FORMATION IN INFANTS

The idea that aspiration of amniotic fluid was the basic cause of the hyaline material has stimulated many investigators to attempt to produce these membranes by intratracheal injections of varying types of foreign material. In 1925, Johnson and Meyer[8] injected Lysol, soap solution, amniotic fluid and egg albumin into the tracheas of rabbits, and were able to produce hyaline membranes only once, and that with egg albumin. Farber and Wilson in 1932[9] and other groups of workers several years later, using materials such as india ink, horse serum, dilute hydrochloric acid, and amniotic fluid, obtained positive results in only a few instances. Blystad, Landing and Smith,[10] however, discovered more frequent lesions in rabbits after the injection of 15-20 c.c. of amniotic fluid, in 1 c.c. amounts over a long period of time. More recent work in this regard has been carried out by Claireaux[11] in England, who reported the production of typical membranes in rats, following intratracheal injection of amniotic fluid previously incubated at 37° C. for eight days.

On the basis of the report by Blystad *et al.*, it would appear that approximately 100-150 c.c. of amniotic fluid would be necessary for membrane formation in a newborn infant, the lung volume of which is only approximately 50 c.c. This large amount of fluid is much more than any infant would be likely to aspirate. Although the experimental observations of Blystad *et al.* and others are strikingly different from those of Claireaux, together they show that under appropriate conditions protein material reaching alveoli by way of the trachea can result in hyaline membrane formation in laboratory animals. It is apparent that these circumstances are so artificial compared to anything that can happen during life that it remains doubtful whether the membranes arise from fluid reaching the lungs by this route.

The hypothesis that the protein forming the hyaline membranes is derived from blood rather than from amniotic fluid is held by several prominent investigators. Arey[12] has stated that intrauterine anoxia may not only result in the aspiration of excessive amounts of amniotic debris in the lungs, but may also be responsible for capillary damage. This damage would then allow for the escape of protein material from vessels, with the resultant formation of eosinophilic membranes. Prematurity is also a factor in increased capillary permeability and, as has been noted, hyaline membrane formation is predominantly a lesion of premature infants. According to this theory, vascular damage, or at least some type of increased capillary permeability, could be the common factor responsible for membrane production in newborn infants, older children and adults.



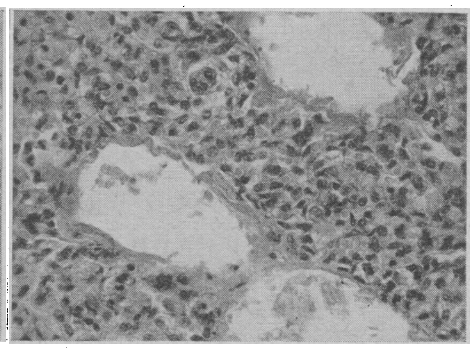


Fig. 1.—Pulmonary hyaline disease. Low-power magnification showing resorption atelectasis with hyaline membrane formation. **Fig. 2.**—Pulmonary hyaline disease. High-power magnification. Small amounts of granular hyaline material are identifiable within some of the collapsed alveoli.

Farber in 1937[13] performed bilateral cervical vagotomies on rabbits, and found that this led to the death of the animals as a result of congestion and pulmonary œdema. Occasionally, bronchopneumonia and hyaline membranes were also noted. This work was repeated in 1951 by Miller[14] and others, and has led to the theory that the proteins forming the membranes are derived from pulmonary œdema fluid which has entered the alveoli after birth. Clinically there are several observations which would tend to support this hypothesis. Most of the infants progress reasonably well immediately after delivery, the rather typical symptoms appearing several hours later. Several workers such as Gruenwald[15] find it difficult to believe that infants whose lungs contain sufficient material at birth to form hyaline membranes several hours after delivery would live for as long a period as they usually do. He has found that the alveolar fluid in cases showing membrane formation is coagulated by histological fixative and has some affinity for stain. This of course does not prove that it is œdema fluid but, as the content of protein in amniotic fluid is relatively low, it suggests that the fluid represents œdema fluid rather than amniotic fluid.

Recently Chapple[16] has commented on a possible hormonal influence on lung permeability. He referred to the results of experiments performed by Lurie, which showed that hormones in some way or other appear to regulate the absorption of various materials in the lungs. He feels that they may therefore play some part in the absorption of amniotic fluid or of œdema fluid. The œstrogen level, which is normally low during the first half of pregnancy, begins to rise at about four and a half months, and the progesterone, which is predominant earlier, follows the œstrogen at a lower level until 24 hours before delivery, when the level falls precipitously. It has been found that œstrogen increases muscle tone and appears to diminish its permeability, while progesterone, on the other hand, relaxes muscle and causes the accumulation of fluid. Labour normally begins when the progesterone level falls. It is obvious therefore that with delivery of the infant by Cæsarean section before labour begins, or in premature labour, a different hormonal situation exists. That the reactions of the newborn in such cases are often quite different is an accepted fact.

Another factor which must be considered in any discussion of the pathogenesis of this disease entity is that of high intrapulmonary oxygen concentration. Davey[17] and several other workers have carried out experiments on acute oxygen poisoning, the presence of eosinophilic membranes in this condition being first described by Pichotka in 1940. Bruns and Shields[19, 20] have produced hyaline membrane formation in a large percentage of laboratory animals exposed to high oxygen concentrations and have described progressive stages in the transition of a normal intact epithelium into cellular degeneration and membrane formation. They suggest that the predisposing factor of fetal anoxia increases capillary fragility, that extrauterine respiration as a precipitating factor initiates bronchiolar and alveolar duct injury, and that aggravating factors such as immaturity and high oxygen concentration further enhance the damaging process with the production of hyaline membranes.

In most of the reports atelectasis has not been encountered in animals subjected to high oxygen concentrations, but recently De and Anderson[21] have described pulmonary collapse in newborn guinea-pigs and rats subjected to these abnormal atmospheric conditions.

Numerous efforts have also been made to link up the presence of hyaline membrane formation in lungs of the newborn with associated fetal inflammation or with various complications which occur in pregnancy or labour. The idea that inflammation played some part in the development arose as a result of the fact that many of the cases first studied also showed bronchopneumonia. This concept has proved to be an unsound one. There also appears to be no correlation of the mother's age, parity, race, serology, or Rh antibodies, or of analgesia, with the presence of the hyaline membranes.

The only factors which bear any constant relationship to hyaline membrane formation are prematurity and Cæsarean section. The explanation of this fact is not well understood, but there is no doubt that those infants delivered prematurely or by Cæsarean section show the highest incidence of pulmonary hyaline membranes. Possible factors which have been shown to lead to membrane formation, and which may be present in this group of infants, are: (1) instability of the semipermeable membranes; (2) high progesterone levels; and (3) possible high oxygen tensions present during the immediate treatment of premature infants.

It is obvious from the preceding discussion that the bulk of the studies carried out to date have dealt chiefly with the examination of the hyaline membrane alone. It would appear that too much stress has been placed upon these lesions, with subsequent neglect of the more important resorption atelectasis. Atelectasis plus hyaline membranes may represent an entity which is quite different from that associated with the simple presence of hyaline membranes in the lungs of infants, older children and adults who die of other causes. Gruenwald has referred to these membranes as "eosinophilic herrings" and is not happy even to accept the fact that they are entirely responsible for the pulmonary collapse. As this problem is studied more intensely, the fact must not be ignored that atelectasis is usually absent in the experimental cases showing hyaline membranes and that it is a constant finding in the newborn and may be present without any evidence of membrane formation.

SUMMARY

Hoccheim in 1903 was the first to describe hyaline membrane formation, while Dick and Pund in 1949 emphasized the importance of the disease process as a primary cause of death. The eosinophilic material is devoid of iron, red cells, amyloid, cholesterol and collagen, but contains the amino acids tyrosine and arginine, with variable amounts of fat and an associated carbohydrate complex. Emphasis is placed on the fact that pulmonary hyaline membranes are encountered in a large number of varied disease processes which occur in adults and older children as well as in the newborn infant. The most important of these disease entities are: (1) influenza and influenzal pneumonia, (2) rheumatic disease, (3) war gas poisonings, and (4) radiation pneumonitis. The suggested etiology is that of vascular injury.

The clinical and pathological features of infants dying of pulmonary hyaline membrane disease are characteristic. The entity is found most commonly in liveborn infants and is present more often in premature than in full-term infants. Death occurs, after a period of normal behaviour, from 1 to 2 hours up to 4 to 5 days after birth. The lungs are of normal size, firm and reddish-purple, showing the microscopic features of resorption atelectasis with irregular layers of homogeneous eosinophilic material coating the alveolar ducts, atria and alveoli.

There are two main schools of thought about the origin of the hyaline membranes. The first deals with the theory that concentrated protein derived from inhaled amniotic fluid produces obstruction and leads to the production of atelectasis after the infant is born. The second is concerned with the derivation of the protein from the blood rather than from aspirated amniotic fluid. The latter is supported by many examples of diseases of older children and adults in which hyaline membrane formation is observed. In all of these diseases, damage to small vascular channels is considered to be the direct cause of the escape of the protein material. It is thought by some workers that high oxygen concentrations with associated vascular and epithelial damage, or hormonal imbalance with coincident increase in vessel permeability, may be important factors in the consideration of the pathogenesis of this disease entity. Others tend to incriminate post-natal œdema fluid as the source of the protein material.

Prematurity and Cæsarean section are the only two factors which bear any close relationship to membrane development.

Up to the present time most of the experimental work carried out has been concerned with the production of the hyaline membranes themselves, the associated resorption atelectasis occupying a secondary position. It would appear that the latter is perhaps the more important of the two, and support is given to the suggestion that resorption atelectasis plus hyaline membrane formation may represent a disease process which is quite different from that associated with the presence of hyaline membranes alone in the lungs of infants, older children and adults.

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